REMARKS

Claims 22 and 23 are amended herein by deleting the word "inhibitor". No new matter is presented.

I. Information Disclosure Statement

Applicant notes that the Examiner did not initial the following references on the Information Disclosure Statement (IDS), but there is no indication as to why these references were not considered and initialed:

1. Supplisson S, Bergman C (1997): Control of NMDA receptor activation by a glycine transporter co-expressed in Xenopus oocytes. J Neurosci 17:4580-90;

2. Tanii Y, Nishikawa T, Hashimoto A, Takahashi K (1991): Stereoselective inhibition by D- and L-alanine of phencyclidine-induced locomotor stimulation in the rat. Brain Res 563:281-284; and

3. Tanii Y, Hishikawa T, Hashimoto A, Takahashi K (1994): Stereoselective antagonism by enantiomers of alanine and serine of phencyclidine-induced hyperactivity, stereotypy and ataxia. J. Pharmacol. Exp. Ther. 269:1040-1048.

Applicant respectfully requests a copy of the PTO/SB/08 Form listing these references, initialed by the Examiner or an indication as to why these references were not considered and initialed.

II. Priority

The Examiner asserts that the current application is not entitled to the benefit of priority as a continuation-in-part of prior U.S. App. Ser. No. 09/365,889, filed August 3, 1999, now U.S. Patent No. 6,361,957, because the subject matter of the current application is directed to different subject matter than what is claimed or recited in the aforementioned patent.

Specifically, the Examiner states that the instant application claims subject matter directed to a composition comprising the particular D-serine transport inhibitor such as D-serine or D-alanine compound, and the above identified U.S. App. Ser. No. 09/365,889, filed August 3, 1999, now US. Patent No. 6,361,957, relates to different subject matter directed to an assay method for identifying antagonists of non-system ASC-mediated D-serine-transport, but fails to disclose the particular compounds such as D-serine or D-alanine compound.

Applicant notes that the statement that the "current application is not entitled to the benefit of priority as a continuation-in-part of prior U.S. App. Ser. No. 09/365,889" is not entirely correct. A continuation-in-part application is defined as "an application filed during the lifetime of an earlier nonprovisional application, repeating some substantial portion or all of the earlier non-provisional application and *adding matter not disclosed* in the said earlier application". MPEP § 201.08. Therefore, by definition, disclosure that is not disclosed in the parent application is permitted in a continuation-in-part application. As long as the continuation-in-part application meets the requirements of 35 U.S.C. § 120, it is permitted to claim the benefit of an earlier filing date for any common disclosure. Thus, Applicant is entitled to the benefit of priority for all subject matter that is commonly disclosed in the present

specification and the prior '889 application.

III. Response to Claim Rejections - 35 U.S.C § 112

A. 35 U.S.C. § 112, 1st Paragraph - Lack of Enablement

Claims 18 and 21 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the scope of enablement requirement.

Applicant respectfully traverses the rejection based on the following.

In making a determination of enablement, the proper inquiry is whether one of ordinary skill in the art would be able to use the claimed invention without undue experimentation. There are several factors which must be weighed and considered to determine whether any necessary experimentation can be considered as undue: (1) the breadth of the claims; (2) the nature of the invention; (3) the state of the prior art; (4) the level of one of ordinary skill in the art; (5) the level of predictability in the art; (6) the amount of direction provided by the inventor; (7) the existence of working examples; and (8) the quantity of experimentation needed to make and use the invention based upon the disclosure. See MPEP § 2164.01(a).

With respect to the nature of the invention, the Examiner states that the rejected claims are broadly drawn to (1) a composition comprising any D-serine transport inhibitor and (2) said composition combined with typical or atypical antipsychotic agents for use in the treatment of schizophrenia. Applicant respectfully submits that present claim 18 is drawn to a composition comprising a selective D-serine inhibitor. Claim 21 depends from claim 18 and therefore is drawn to a composition wherein the D-serine inhibitor is selective and is present in an amount

sufficient to augment NMDA-mediated neurotransmission and combined with an atypical or typical antipsychotic agent. The Declaration submitted on October 14, 2004, explains the significance of this element of the claims. An executed copy of the previously filed unexecuted Declaration, is submitted herewith for the record.

With respect to the state of the art and the level of skill in the art, the Examiner defines the state of the art with regard to the use of D-serine transport inhibitors for the treatment of schizophrenia as underdeveloped and the level of skill in the art as low. On the contrary, Applicant respectfully submits that at the time of the present application, it was known to those of ordinary skill in the art that agents which stimulated NMDA receptors via the glycine/D-serine binding site were useful in the treatment of schizophrenia as supported by the present specification and numerous publications, for example, references 1-20, listed below,[1] and including Tsai cited by the Examiner. The Javitt patent (U.S. Patent No. 5,837,730, "Treatment of Negative and Cognitive Symptoms of Schizophrenia with Glycine Uptake Antagonists") further taught that amino acid levels in brain could be modulated indirectly, through administration of antagonists of amino acid transport. The prior parent application, No. 09/365,889, now U.S. Patent No. 6,361,957 (the '957 patent), demonstrated the existence of a previously unknown D-serine transporter that regulated brain D-serine levels. Thus Applicant submits that the state of the art was sufficiently developed and not underdeveloped as asserted by the Examiner.

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[1] References 1, 2, 8 and 10 were previously submitted with the IDS filed on March 25, 2005 and are of record. References 4-7 listed below were previously provided with the Declaration filed on October 14, 2004 and are of record.

Further, contrary to the Examiner's statement, the level of skill in this art is high.

This application differs from the prior art in that the use of compounds that block D-serine transport, leading to indirect NMDA stimulation is claimed, rather than use of compounds that bind directly to the NMDA receptor. Applicant also refers the Examiner to the Declaration under 37 C.F.R. § 1.132 previously filed on October 14, 2004 which also addresses the predictability in the art and guidance and examples provided in support of the enablement of the present invention. Thus, since all other elements of the enablement were already taught by multiple sources at the time of the filing date of the present application, the only issue is whether the present specification enables development of compounds that block D-serine transport via the novel transporter.

Applicant submits that this issue is divisible into two parts. The first question is whether all the steps from the description of the structure of compounds within the scope of the present invention to clinical application constitute undue experimentation, and second whether the steps from a screening assay to the identification of specific compounds within the scope of the invention constitutes undue experimentation, which also relates to the factors (5)-(7) above, i.e., of the level of predictability in the art; the amount of direction provided by the inventor, and the existence of working examples, respectively. In this regard, Applicant submits herewith a Supplemental Declaration under 37 C.F.R. § 1.132, which establishes that based upon the present specification, one of ordinary skill in the art could readily practice the claimed invention and determine compounds within the scope of the claims for use in the claimed compositions and methods. The Supplemental Declaration includes over 200 compounds generated using

standard techniques with standard skill in the art that are within the scope of the present claims which were -obtained by the assay method described in the present specification. Therefore, the Supplemental Declaration demonstrates that the specification provides sufficient guidance and direction for one or ordinary skill in the art to be able to practice the claimed invention.

With respect to the issue of whether undue experimentation is required to practice the claimed invention, Applicant previously pointed out that the necessary screening for compounds within the scope of the invention is not "undue" in the "Remarks" in the Amendment filed on October 14, 2004, which are incorporated herein by reference.

The Examiner asserts that practicing the claimed invention would require undue experimentation because one of skill in the art would have to first envision a selective D-serine transport inhibitor, an antipsychotic agent, a pharmaceutical carrier, a dosage for the inhibitor, the duration of treatment, route of treatment, etc., then test specific inhibitors in the model system to determine whether or not it is effective for augmenting NMDA-mediated neurotransmission, thus treating schizophrenia, and one would need to test for side effects and toxicity. It is the Examiner's position that further tests and experimentation would be necessary depending on whether or not the first tests with the first agent were successful.

Applicant respectfully submits that the Examiner characterizes the process for developing a compound from initial general description to clinical utility. However, this is not the proper inquiry for the standard of enablement for a patent application. Under 35 U.S.C. §112, first paragraph, the specification of a patent application must "contain a written description of the invention, and of the manner and process of making and using it, in such full,

clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same . . . ." In other words, the specification must provide sufficient information such that one of skill in the art could make and use the invention.

The present specification provides sufficient enablement for the present claims consistent with and similar to other issued patents. For example, in the Tsai application now patent number 6,228,875, issued May 8, 2001, which is provided as a reference against the present application, the claims are directed to the use of an agonist of the glycine site of an NMDA receptor for the treatment of a neuropsychiatric disorder characterized by attenuated NMDA neurotransmission in a patient. Claim 7 of the Tsai patent recites:

> A method for treating a neuropsychiatric disorder characterized by attenuated NMDA neurotransmission in a patient, the method comprising administering to a patient diagnosed as suffering from the neuropsychiatric disorder a pharmaceutical composition comprising a therapeutically effective amount of an agonist of the glycine site of an NMDA receptor, wherein: the agonist is selected from the group consisting of D-alanine, a salt of D-alanine, an ester of D-alanine, alkylated D-alanine, a precursor of D-alanine, D-serine, a salt of D-serine, an ester of D-serine, alkylated D-serine, a precursor of D-serine, D-cycloserine, a salt of D-cycloserine, an ester of D-cycloserine, a precursor of D-cycloserine, and alkylated D-cycloserine; the pharmaceutical composition is substantially free of D-cycloserine when the agonist is D-alanine, a salt of D-alanine, an ester of D-alanine, an alkylated D-alanine, or a precursor of D-alanine; and when the agonist is D-cycloserine, a salt of D-cycloserine, an ester of D-cycloserine, a precursor of D-cycloserine, or alkylated D-cycloserine, the pharmaceutical composition comprises an amount of the agonist equivalent to 105-500 mg of D-cycloserine.

To practice the claimed method of Tsai, one would first have to synthesize a large number of compounds (salts, esters, etc.), test for side effects and toxicity, determine dosage,

duration of treatment, route of administration, etc. One would also then need to determine the magnitude of the side effects and toxicity of utilizing the agonist. One would then have to determine whether or not the magnitude of the side effects could be reduced by increasing or decreasing the dosage of the derivative while retaining the functional aspect. Once the functionality to toxicity ratio was maximized, one would need to determine whether or not the salt, ester, alkylated or precursor compound used was of sufficient benefit that it would serve as useful for treating schizophrenia. If not, one would need to select another compound and repeat the process.

Further, the claims of Tsai do not even specify specific disorders. Thus, one would have to test whether a given neuropsychiatric disorder is characterized by attenuated NMDA neurotransmission in a patient, and then conduct all the tests listed above.

In view of the above, these are standard procedures in the art which require a significant amount of tests and experimentation; however such experimentation is routine in the art and is not considered as undue. Therefore, the amount of experimentation needed to practice the present invention as claimed is commensurate with the amount of experimentation that is routine in the art. The present claims and description do not differ significantly from what has been allowed in countless prior applications directed to a method of treatment. According to the Examiner's logic, treatment claims would be allowed only after FDA approval, which clearly is not the law and is not the position taken by the USPTO before now.

Based upon a presumption of validity under 35 U.S.C. § 282 of these claims of the '875 patent, Applicant submits that the present specification is at least equally enabling for the

claimed D-serine transport inhibitors based upon the description provided in the present specification.

Additionally, the argument that undue experimentation would be required to generate compounds that function as D-serine transport antagonists is further obviated by the Declaration demonstrating that such compounds can easily be synthesized based upon the teachings of the present specification. Such evidence should be considered by the Examiner.

Applicant further notes that the present claims are based not only by the synthesis of the specific compounds disclosed in this application, but also by the prior '957 patent from which this application derives. Thus, this application is the end point of a search for a novel D-serine transporter in brain, rather than a hunting license for new antagonists. Approval for use of this class of agent for treatment of conditions known to involve NMDA receptor dysfunction is an appropriate reward for being the first to discover a novel transporter in the brain related to NMDA receptor function.

In view of the above, Applicant respectfully requests withdrawal of the rejection under 35 U.S.C. § 112, 1st paragraph.

B. 35 U.S.C. §112, 2nd Paragraph - Indefiniteness

1. "A typical or atypical antipsychotic agent"

Claims 18 and 21 are rejected under 35 U35 U.S.C. §112, second paragraph, as allegedly being indefinite. The Examiner states that the phrase "a typical or atypical antipsychotic agent" is vague and indefinite and it is not clear what other compounds this term encompasses, since one of ordinary skill in the art could not ascertain the metes and bounds as

to the "typical or atypical antipsychotic agent", and the specification does not provide a standard for ascertaining the phrase.

Applicant respectfully traverses the rejection based on the following. First Applicant notes that the phrase "a typical or atypical antipsychotic agent" is only recited in claim 21 and therefore the rejection of claim 18 is improper. As for claim 21, Applicant notes that the term "atypical antipsychotic agents" is a term of art used to refer to a class of drugs known to alleviate positive symptoms and improve negative symptoms of schizophrenia and other psychoses to a greater extent than conventional antipsychotic agents. See, e.g., The Merck Manual, 17th Ed., page 1569-1571. Further, Applicant notes that the terms "typical" and "atypical" are used in the same context in the Tsai patent cited as a reference against the present application, thereby providing evidence that these are commonly used in the art and are understood by those of ordinary skill in the art. Therefore, Applicant submits that the present claim language is readily understood by those of ordinary skill in the art and is sufficiently definite.

Accordingly, Applicant respectfully requests withdrawal of this ground for rejection under 35 U.S.C. § 112, 2nd paragraph.

2. "Selective D-serine Transport Inhibitor"

Claims 18-24 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. The Examiner states that the term "selective" in the phrase "selective D-serine transport inhibitor" is vague and indefinite as it is not clear what other compounds this term encompasses, since one of ordinary skill in the art could not ascertain the metes and bounds as

to the "selective", and the specification does not provide a standard for ascertaining the term.

Applicant respectfully traverses the rejection and submits that the term "selective" is commonly used in the pharmaceutical arts and therefore it is a term of art which is to be given its plain and ordinary meaning that is consistent with the specification and the interpretation it would be given by those of ordinary skill in the art. For example, Prozac™, is a well known drug which is classified as a selective serotonin transport inhibitor (SSRI). A drug that is "selective" is well understood by those of ordinary skill in the art as being an agent that has a major effect at a specific target of interest, while having no more than a minor effect at other relevant targets. Thus, one of ordinary skill in the art would be able to readily ascertain the meaning of the term "selective" as used in the present claims and to readily ascertain the scope of the present claims according to the plain an ordinary meaning of the term as used by those of ordinary skill in the pharmaceutical arts.

Applicant also notes that claims 19-20 and 22-24 recite specific selective D-serine transport inhibitor compounds that block uptake of D-serine by a novel transporter as described in the specification, which is readily understood by those of ordinary skill in the art. Therefore, the rejection as to these claims on this basis is clearly improper.

Accordingly, Applicant respectfully requests withdrawal of this ground for rejection.

3. "Hydrophobic Group"

Claim 22-24 are further is rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite based on the phrase "hydrophobic group", which is said to be unclear.

Applicant respectfully traverses the rejection. Applicant submits that the term "hydrophobic" is to be given its plain and ordinary meaning that is consistent with the specification and the interpretation it would be given by those of ordinary skill in the art. Further, Applicant notes that claim 24 recites specific hydrophobic groups and therefore the meaning of this term is readily understood by those of ordinary skill in the art.

Accordingly, Applicant respectfully requests withdrawal of this ground for rejection.

4. "Alanine Inhibitor Compound"

Claims 22-24 are further rejected under 35 U.S.C. §112, second paragraph, as lacking antecedent basis for the recitation "alanine inhibitor compound" in claim 22.

Claim 22 is amended herein to recite the "serine or alanine compound", thereby obviating the rejection.

Accordingly, Applicant respectfully requests withdrawal of this ground for rejection.

5. "Substituted Phenyl Group"

Claim 24 is further rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. The Examiner states that the claim recites the phrase "substituted phenyl group", which is vague and indefinite, as it is not clear if the phenyl group is "substituted" with alkyl, aryl, heteroaryl, halogen etc.

Applicant respectfully traverses the rejection. The term "substituted" may be consider broad, but not indefinite. The claim language is clear as written in that the term "substituted phenyl group" should be given its ordinary and plain meaning of a phenyl group that may have

substituents as would be readily understood by those of ordinary skill in the art.

IV. Response to Claim Rejections - 35 U.S.C § 102

A. Takuma et al

Claims 20, 22-24 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Takuma et al (JP 08026986, PTO-892).

According to the Examiner, Takuma et al discloses compositions containing D-serine esters preferably the ethyl ester or their pharmaceutically acceptable salts as active ingredients and pharmaceutically acceptable carrier and that the compositions are useful for the treatment of schizophrenia. See Abstract.

Applicant traverses the rejection. First Applicant notes that claims 20, 22 and 24 depend from claim 18 which is not included in the rejection. Claims 20, 22 and 24 depend from claim 18 and are distinguished over Takuma et al for at least the same reasons as claim 18. Further, Takuma et al does not disclose the use of a selective D-serine transport inhibitor as recited in independent claim 18, upon which the rejected claims depend. Specifically, Takuma et al teaches only that D-serine esters act as precursors to D-serine, which acts at the modulatory site of the NMDA receptor complex. Based upon the attached computer generated English translation of Takuma et al at paragraph [0018], the disclosed D-serine ester acts at the glycine binding site of the NMDA receptor, which is different from the claimed selective D-serine transport inhibitor of the present application. The claimed selective D-serine transport inhibitor blocks D-serine transport but does not bind to NMDA receptors. Therefore, the present claims

are directed to compounds that act at a totally different site. Neither D-serine nor D-serine ethyl ester is an antagonist of D-serine transport. In this regard, Applicant refers the Examiner to the attached paper by McBain et al which demonstrates that modifications of the D-serine molecule leads to the loss of binding at the NMDA receptor. Further, the data provided in the present specification and the Declaration show that the recited serine and alanine compounds block D-serine transport.

In view of the above, Takuma et al cannot be said to anticipate the presently claimed invention. Accordingly, Applicant respectfully requests withdrawal of the rejection.

B. Tsai et al

Claims 20, and 22-24 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Tsai et al (WO 99/52519, PTO-892).

According to the Examiner, Tsai et al disclose pharmaceutical composition containing D-alanine, D-serine or modified version of the amino acid such as salt, ester, alkylated form for the treatment of schizophrenia. Pharmaceutical compositions for oral administration are prepared in pharmaceutically acceptable carriers such as water or other aqueous vehicles. See page 14, lines 23-30. Thus the Examiner concludes that Tsai anticipates the current invention claims 18, 20, 22-24.

Applicant respectfully traverses the rejection. This rejection is essentially the same as the previous rejection over Tsai in the Office Action dated April 14, 2004. Therefore, Applicant traverses the rejection for the reasons set forth in the response filed on October 14, 2004,

which are incorporated herein by reference. Further, the present claims are directed to a selective D-serine transport inhibitor, which is not disclosed, taught or suggested by Tsai et al for the reasons previously set forth. Further, Tsai does not provide an assay for determining which agent falling within the broad genus would actually serve as an effective D-serine transport inhibitor and further, makes no mention of D-serine transport. Therefore, it cannot be said that Tsai et al anticipates the presently claimed invention.

Accordingly, Applicant respectfully request withdrawal of the rejection under 35 U.S.C. § 102.

C. Javitt

Claims 18 and 21 are rejected under 35 U.S.C. § 102(b) as being anticipated by Javitt (WO 97/20553, PTO-1449).

According to the Examiner, Javitt discloses a composition comprising glycyl alkyl esters, glycylalkylamides, such as glycyl-dodecylamide for the treatment of schizophrenia by augmenting NMDA receptor mediated neurotransmission. Thus, the Examiner concludes that Javitt anticipates instant claims 18 and 21.

Applicant respectfully traverses the rejection. Javitt discloses glycine transport inhibitors, but does not make reference to D-serine transport inhibitors. The WO publication is primarily directed towards glycyl-dodecylamide (GDA) as a glycine transport inhibitor. Although GDA inhibits glycine as well as D-serine transport, the present claims are based upon the relative effects of GDA, D-Serine and D-alanine DA. The WO publication does not disclose,

teach or suggest that GDA also acts as a selective D-serine transport inhibitor. On the contrary, GDA is a mixed glycine/serine transport inhibitor, whereas a selective inhibitor is claimed in the present application.

Further, the WO publication does not teach or suggest a composition comprising an effective amount of a selective D-serine inhibitor for treating schizophrenia.

V. Claim Rejections - 35 U.S.C § 103

Claim 19 is rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Javitt (WO 97/20553, PTO-1449), in view of Tsai et al.

Javitt is as discussed above. The Examiner states that Javitt does not expressly teach a composition comprising D-alanine dodecylamide (d-ala-da) for the treatment of schizophrenia.

Tsai et al is relied on for the disclosure of a pharmaceutical composition containing D-alanine or modified version of the D-alanine such as salt, ester, alkylated form for the treatment of schizophrenia.

It is the Examiner's position that it would have been obvious to a person of ordinary skill in the art at the time of invention to substitute glycyl dodecylamide in the composition of Javitt with D-alanine dodecylamide because Tsai teaches D-alanine or modified version of D-alanine can be used in the composition for treating schizophrenia, and D-alanine dodecylamide is a modified version of D-alanine. One of ordinary skill in the art at the time of invention would have been motivated to substitute glycyl dodecylamide with D-alanine dodecylamide with the expectation of obtaining a pharmaceutical composition which has higher efficiency in treating

schizophrenia because Tsai teaches that the dodecylamide compounds of amino acid such glycine have higher potency than esters of glycine in treating schizophrenia.

Applicant respectfully traverses the rejection and submits that the references, whether taken alone or in combination, do not teach or suggest the present invention as recited in the claims. First, claim 19 depends from claim 18, which is not included in the rejection and therefore claim 19 is distinguished over the references for at least the same reasons as claim 18. Further, as discussed above, neither one of Javitt or Tsai et al teach a selective D-serine inhibitor, much less the specifically claimed D-alanine dodecylamide. Therefore, the references do not teach or suggest all elements of the claimed invention and even if combined, the claimed invention would not have been achieved.

Even further, d-ala-da provided unexpectedly superior results in that it showed a different pattern of activity in the inventive assay than GDA or d-ser-da and inhibited amphetamine-induced hyperactivity whereas GDA did not. Thus, D-ala-Da would be expected to have superior efficacy relative to other compounds, which would not have been expected based upon the disclosures of Tsai and Javitt.

In view of the above, the presently claimed invention is not rendered obvious by the cited references. Accordingly, Applicant respectfully requests withdrawal of the rejection under 35 U.S.C. §103.

VI. Request for Interview

Applicant requests an Interview to discuss the present application, the prosecution

history and evidence of record. The Applicant feels that an Interview is warranted to facilitate and expedite prosecution, since a new Examiner has been assigned to the application.

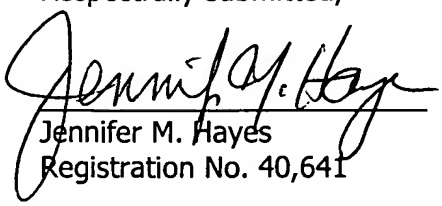
The Applicant is available for a personal Interview on February 22, 2006, and therefore has requested an Interview on this date. During a telephone communication, Examiner Shobha Kantamneni indicated that she would be available for an Interview on this date. Applicant has also submitted a Request for Suspension of Action for three months herewith, to ensure that the Applicant will have an opportunity to discuss the application with the Examiner before the next Action.

VII. Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,



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APPENDIX

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